UREMIC HEMIPLEGIA, WITH CHANGES IN THE NERVE CELLS OF THE BRAIN AND CORD, AND RECENT PRIMARY DEGENERATION OF ONE CENTRAL MOTOR TRACT.[1]

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Some of the effects of the disorder known as uremia upon the nervous system have been well recognized in recent years, although it is not so long ago that this was denied. Of the different manifestations of this disease none have been of more interest or have excited more study than the hemiplegia produced by the uremic condition. In spite of the large number of cases with necropsy, and of experiments upon lower animals, the cause of this disease still remains in doubt.

The usual findings at necropsy have been more or less edema of the brain substance and its membranes, and at times dilatation of the ventricles. A number of cases have been reported, however, where no edema was found. (Level, Chauffard and Lancereaux.) The edema may be symmetrical, it may be localized to the side of the brain opposite the hemiplegia (Pätsch, Charpentier), or it may be on the same side as the hemiplegia (Charpentier). A case was reported by Mann where in a right hemiplegia preceded by Jacksonian convulsions, the left ventricle was distended to about three times the size of the right ventricle.

It is hard to explain why a bilateral edema should produce a unilateral paralysis, or why the edema should produce paralysis at all. In the great number of cases of uremia which come to autopsy, in which there are no nervous symptoms, edema of the brain or membranes is a common finding.

The well known experiments of Raymond may perhaps throw some light upon the physiology of this condition. The left superior cervical ganglion was removed from a rabbit and several days later the vessels at the hilum of the kidney were ligated, producing an artificial uremia. Convulsions occurred and were limited to the right side of the body. When the right ganglion was removed and the vessels tied, the convulsions were limited to the left side; or, the uremic disturbances showed themselves on the side governed by the cerebral hemisphere, the vessels of which had been paralyzed by the removal of the ganglion. At the necropsy, however, there was found a diffuse bilateral edema.

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As a result of more recent research the theory that edema is the primary cause of uremic hemiplegia has been abandoned, and it is believed that definite organic changes in the central nervous system are the causes of this condition. Such changes, however, have not been heretofore described.

The cellular changes in the central nervous system in experimental uremia of dogs, have been studied by Acquisto and Pusateri. In the anterior horn cells of the spinal cord these investigators found loss of peripheral chromatic bodies, while the perinuclear bodies had undergone granular disintegration. In the cerebral cortex different stages of chromatolysis were noted. In some cells the peripheral chromatic bodies and the dendritic processes were normal, while in the perinuclear zones there was advanced chromatolysis. Other cells were homogeneous, and their nuclei dark and indistinct.

Sacerdotti and Ottolenghi also examined the central nervous system in dogs dying four to seven days after ligature of both ureters. By Golgi's method they demonstrated varicose atrophy of the dendrites, while the axis cylinder processes remained normal. The lesions were most marked in the cerebral cortex, where all the cells were affected, but were also abundant in the pes hippocampus. Nissl's stain failed to show the chromatolytic changes in the cortical cells described by Acquisto and Pusateri.

Donetti examined by Golgi's and Nissl's method the central nervous system of rabbits dying from uremia after bilateral nephrectomy. By Golgi's method he found varicose atrophy of dendrites with other less definite changes in the cortical and cerebellar cells. By Nissl's method there were no distinct alterations in the cortical cells. In the medulla and the cord the nuclei of the large cells were very often eccentric, the chromatic substance was reduced in amount, the bodies were finely fragmented, and many cells contained vacuoles. He does not believe that these lesions are characteristic of uremia.

Gabbi, as a result of bilateral tying of the ureters, found in the cerebral cortex of guinea pigs and rabbits, in most of the cells a perinuclear chromatolytic process with a homogeneous condition of the nucleus. In the medulla there were examples of peripheral chromatolysis. With Golgi's method varicose atrophy of the nerve cells was found. Some of the cells in the anterior horns were deformed.

Ewing studied microscopically the nerve cells of the brain and cord of six cases of uremia. In none of his cases were there any accompanying paralysis of the upper and lower limbs of either side, except in one case where one arm was paralyzed. He came to the following conclusions: "Uremia as it occurs in the human subject is associated with rather marked changes in the chromatic substance of the nerve cells, but these changes are very irregular in character and distribution. As a rule the spinal cells are but little changed in uncomplicated cases. The lesions are most marked in the medullary nuclei, especially in the nuclei of the tenth nerve and above, as well as in the deeper cells throughout the medulla. Here nearly every variety of chromatolysis may be observed, excepting very advanced or complete bleaching of the cells, which is rare.

"The cortical cells are usually better preserved than might be expected from the very marked cerebral symptoms of fatal and prolonged uremia. In the case dying with severe convulsions the cortical as well as the medullary lesions were most marked.

"The condition of Purkinje's cells was very uniform in the cases examined, the chromatic bodies of these cells being very irregular in size and shape, and considerably deficient in number.

"The effects of the pial edema could not be distinctly traced in the cortical cells.

"No distinct or uniform nuclear changes were detected in these cases, although the nuclei were often abnormal in appearance. The achromatic substance of the cortical archyochromes frequently appeared greenish and opaque, suggesting an early stage of pigment degeneration.

"The most advanced cellular alteration of the series were seen in the nuc. X and deeper cells (nuc ambiguus), in the case in which severe dyspnea had been the chief complaint for five days before death.

"In general, it seems reasonable to conclude that the lesions of the nerve cells in uremia are largely referable to local influences and partly also to general toxemia. Among such local influences may be suggested, (1) altered condition in the peripheral fibers of the cells; (2) local circulatory disturbances; (3) overaction of particular groups of nerve cells; (4) and possibly also the effects of pyrexia.

"Finally, in the above cases, there was a fair parallelism between the grade of cellular change and the general severity of the symptoms."

So far as I know there are no cases of uremic hemiplegia with changes in the nerve cells and in the central motor system on record. The first case I have to report is as follows:

L. W., seventy-one years old, washerwoman, was admitted to the Philadelphia Hospital, June 6, 1903, service of Dr. C. S. Potts, from the outwards. The patient had complained of weakness for some time, and suddenly lost power of her left side. No history of her previous condition could be obtained. The following notes were made by Dr. Potts, to whom I am also greatly indebted for the post-mortem material.

"Patient is dull mentally, but can understand and does answer questions intelligently. The mouth is drawn toward the right side. She can close both eyes equally well, but there is a weakness of the occipito-frontalis and corrugator supercillii muscles on the left side. The left arm and leg are completely paralyzed. Sensation is not altered. The biceps and triceps jerks are present and equal on both sides. The knee-jerks are prompt and equal on either side. The Achilles jerks are present. No ankle clonus on either side. Both plantar reflexes are active, more so on the left side, where the great toe is slightly extended. The pupils are equal, and react sluggishly to light. There is no conjugate deviation of the eyes, and no difficulty in swallowing."

The patient gradually grew weaker and died fourteen days after the onset of the paralysis. The temperature varied between 97° and 98° F. during her illness. The urine examination was undoubtedly made, but the record has been unfortunately lost from the history sheet.

The necropsy was performed by Dr. C. H. Bunting, who made the following notes regarding the patient's kidneys: "The kidneys are small, the capsule is thickened, leaving a granular, roughened surface when stripped. On section, the cortex is narrow, the striæ irregular and the glomeruli are injected and prominent."

The pathological diagnosis was:

Arteriosclerosis, chronic diffuse nephritis, cardiac hypertrophy and dilatation, chronic interstitial pleuritis and enterocolitis.

There was no note made of edema of the membranes of the brain or cord. The ventricles were opened and the specimens put into Orth's fluid. Horizontal sections made show no gross lesions, and a careful examination showed no small lacunæ, nor areas of softening as described by Marie.

Microscopically the changes in the nerve cells as stained by the thionin stain are as follows:

Lumbar region.—The cells here are similar to those in the cervical region. The cells of the column of Clarke are much degenerated. The chromophilic elements in many of the cells have entirely disappeared, and are replaced by a mass of fine granular yellow pigment filling up the whole cell body. In most of the cells the nuclei are at the periphery.

Cervical region.—The cells of the anterior horns are intensely pigmented, which is not remarkable considering the age of the person, which was seventy-one years. Some of the cells are probably atrophied, the nuclei are not displaced and the alteration in the cells is slight.

Paracentral lobule.—The Betz cells of the left paracentral lobule are intensely pigmented. In some of the cells the pigment fills the whole cell body, and in these cells the nucleus cannot be observed. The Betz cells of the right paracentral lobule are similar to those in the left paracentral lobule, but the alteration is more intense than in the left. In some cells chromatolysis and peripheral displacement of the nucleus without an excessive amount of pigment, are found.

Cerebellum.—Many of the cells of Purkinje are swollen, and in some the nucleus is eccentric and the chromophilic elements are more or less broken up. Pigmentation of these cells is not pronounced.

Medulla.—The cells of the nucleus ambiguus of each side are in fair condition, however here and there a much altered cell is found. In these cells the nucleus is displaced to the periphery and the chromophilic elements are disintegrated. Nerve cells from the frontal, temporal and occipital regions do not show any distinct pathological changes.

The Weigert hematoxylin and acid fuchsine stains show no changes in the spinal cord.

In the lumber region degeneration as shown by the Marchi method is present in the left crossed pyramidal tract. It is slight, but unmistakable. In the cervical region the degeneration in the crossed pyramidal tract of the left side is greater than that in the lumbar region. It is moderate in degree, and is such as would be found in a primary degeneration of short duration. It is, however, unmistakable and is confined to the left crossed pyramidal tract. There is much less intense degeneration in the right direct pyramidal tract.

In the right pyramid there is still degeneration by the Marchi method, but it is much less intense than in the left crossed pyramidal tract in the cervical region. Degeneration by the Marchi method is still shown in the middle portion of the foot of the right cerebral peduncle. It is much less intense than in the left crossed pyramidal tract of the cervical region.

In the right internal capsule by the Marchi method a number of degenerated fibers can be seen, but these are so few in number that it is impossible to state definitely that there is degeneration of the motor fibers.

The Betz cells of the paracentral lobule show no change by the Marchi method.

Case II. W. E., seventy-seven years old, was admitted to the Philadelphia Hospital August 31, 1903, service of Dr. Wm. G. Spiller. The notes made by Dr. Spiller on the same day are as follows: "The patient is completely unconscious. The left palpebral fissure is larger than the right. The left pupil is larger than the right. The lower distribution of the left seventh nerve is paralyzed. The man makes no effort to draw up either side of the mouth when he is stuck with a pin. The left upper limb is completely paralyzed and is spastic at the elbow. The biceps, triceps and wrist reflexes are exaggerated on both sides. Both lower limbs are somewhat spastic. The left lower limb is almost completely paralyzed. When stuck with a pin he moves the left toes slightly. Both patellar jerks are present, but diminished. The right upper and lower limbs are moved voluntarily, and also when he is stuck with a pin."

The patient's temperature on admission was 101.4° F., but was normal when he died four days after the onset of his paralysis. Here also the urine examination report was lost.

The necropsy was performed by Dr. John Funk, who made the following notes: "The kidneys are small and show fetal lobulation. The capsule strips with difficulty, revealing a granular area. The cortex is narrow, and is diffused into the medullary portion, which is inconspicuous. The pyramids are visible only here and there. The pelvis contains considerable fat." The other pathological diagnoses were: Fibroid myocarditis, chronic endarteritis and atheroma of the vessels at the base of the brain.

Here also there was no note made of the edema of the cerebral or spinal membranes. Horizontal sections of the brain show no gross lesions.

There is no degeneration of either crossed pyramidal tract by the Weigert hematoxylin, acid fuchsine or Marchi methods.

The nerve cells of the anterior horns of the lumbar region are about normal and not nearly so much pigmented as one might expect in a person so old as seventy-seven years. Chromatolysis is seen in some of these cells, but is not intense.

The nerve cells of the anterior horns of the cervical region are much like those in the lumbar region, except that they are more pigmented.

Many of the Betz cells of the left paracentral lobule are nearly normal, but some are in a state of chromatolysis.

The changes in the cells of the Purkinje are slight. Some of the nuclei are displaced and there is a slight chromatolysis.

The cells of the nucleus ambiguus are in a very good condition, many of them are deeply pigmented and here and there some cells are much altered.

We have here, therefore, two cases of hemiplegia of uremic origin where macroscopically no gross lesion was found. In the first case the paralysis lasted 14 days before death, while in the second case the man lived only 4 days after the onset of the hemiplegia. The changes in the nerve cells as shown in the Betz cells of the paracentral lobule in the first case, while intense on both sides, were distinctly more so on the side opposite the paralysis. The alterations in these cells were not uniform, except that an intense yellow pigmentation was present in nearly all the nerve cells. The cells of the anterior horns of the spinal cord were not much altered, but here too the yellow pigment was abundant.

The degeneration of the motor fibers as shown by the Marchi method was traced from the lumbar region of the spinal cord to the internal capsule.

The degeneration, while not intense, was unmistakable, and was of such a character as would be expected in a primary degeneration of recent origin, in this case fourteen days. It was most marked in the crossed pyramidal tract of the cervical region, and became less intense in the medulla, and cerebral peduncle, and in the internal capsule it was hard to find traces of it.

The degeneration was essentially a primary degeneration, i.e., not due to any destruction of the fibers in a limited part of their course, and was in association with the changes in the nerve cells in the motor cortex. That the degeneration was found only in the motor fibers of one side, is explained by the more intense changes in the cortical cells belonging to these fibers, and it is a fair presumption that had the uremic poison or poisons had time to act further, there would have been also a primary degeneration of the motor fibers of the opposite side.

I hardly expected to find recent degeneration by the Marchi method in the second case, for here the hemiplegia was only of four days' duration. Changes were found, however, in the nerve cells of the cortex, cerebellum, medulla and the anterior horns of the spinal cord, but these were not as intense as in the cells of the corresponding regions of the first case.

It is hard to explain why the alterations in the nerve cells were more intense on one side of the cortex, except by the theory of *locus minoris resistantiæ*, which is hardly an adequate explanation.

As a result of the study of these cases we must come to the conclusion that a toxic process like uremia may produce definite changes in the nerve cells of the brain and spinal cord, and that these changes may be more marked in the motor cells of the cortex, and in association with these alterations in the nerve cells of the motor cortex we may have a primary degeneration of the motor fibers, provided the duration of the hemiplegia is long enough.

The effects of other toxic processes upon the central nervous system have been carefully studied, and changes in the nerve cells of the brain and cord have been repeatedly observed. These alterations, however, have not been uniform or characteristic, and it may be that the findings in the first case may have an important bearing on the future study of these conditions.

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